

## REMARKS

Claims 53-67 and 70-72 presently are pending and under consideration. Applicant's responses to the comments and rejections articulated in the Office action are set forth below. Moreover, the Examiner is cordially invited to contact the undersigned attorney with any further questions.

### *Rejection of Claims 53-59, 62-67, 70, and 71 Under 35 U.S.C. § 103(a)*

According to pages 5-9 of the outstanding Office action, claims 53-59 and 62-67, 70, and 71 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,437,267 to Weinstein *et al.* (hereinafter "Weinstein") and Published U.S. Patent Application Publication No. US 2001/0004644 A1 to Levin (hereinafter "Levin") in view of Ward-Smith in Nasal Spray Testing, Pharmaceutical Technology Europe (2002) pages 1-9 (hereinafter "Ward-Smith"). Pages 2-4 of the Office action contain the Examiner's further contentions concerning the rejection of claims 53-59 and 62-67, 70, and 71 under 35 U.S.C. § 103(a).

Applicant's traverses to the rejection under 35 U.S.C. § 103(a), and traverses to the Examiner's contentions, are set forth below:

#### 1. The Office Action's Reliance on "Obvious to Try" as the Basis for Rejection of the Pending Claims Under 35 U.S.C. § 103(a) is in Violation of Controlling Federal Circuit Precedent.

Despite the fact Applicant has explained for the benefit of the public and the Patent Office that intranasal spray plume geometry affects absorption of the drug administered, that there are a multitude of possible spray plumes that could be tried, that the art cited in the Office action provides no guidance as to which spray plume would be effective for nasal delivery of the opioid composition required by the claims, that the art cited in the Office action provides no particularized guidance as to which of many spray plume parameters should be adjusted to achieve superior absorption of the particular composition required by

the claims, and pending claim 53 is focused on a particular spray plume characterized by its own unique features, the Office action asserts on page three that:

- it would have clearly been obvious to try variable spray plumes for optimal therapeutic effect, i.e., increased surface area of the active agent to the intranasal passages [emphasis added]
- in the well-known art of pharmacokinetics, it would well be within the purview of the one of skill to engineer and/or manipulate the configuration of the device in such a way as to achieve the desired spray plume.

The standard applied by the Office action for determination of obviousness under 35 U.S.C. § 103(a) is in violation of controlling Federal Circuit precedent. For example, in a opinion issued just prior to mailing of the Office action, **the Federal Circuit stated that a *prima facie* case of obviousness under 35 U.S.C. § 103 is not established by “vary[ing] all parameters or try[ing] each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.”** *In re Kubin* (Fed. Cir. 2009), 08-1184.

As discussed previously and acknowledged by the Examiner, spray plume geometry is an important feature that impacts how quickly and how much of the therapeutic agent is absorbed through the nasal mucosa following intranasal administration using a unit-dose delivery device. Moreover, spray plumes can have widely different features, e.g., differences in the droplet size at specific distances from the end of the spray nozzle, and differences in the width (i.e., the span) of the spray plume as it advances from the end of the spray nozzle. Each of these features have a profound effect on the pharmacokinetics of drug delivery.

None of Weinstein, Levin, or Ward-Smith provide any particularized guidance as to which spray plume parameters are critical, nor do these references provide any direction as to which of the many possible combinations of such parameters would produce a spray plume superior for administration of an opioid containing intranasal pharmaceutical composition. As a result, the skilled artisan, at the time of filing of Applicant's application, would be left to varying all parameters or trying each of numerous possible choices. Indeed,

based on the multitude of possible spray plumes and lack of instruction provided by the art cited in the Office action, there is no reason that the skilled artisan would know to select the spray plume required by claim 53 having a “Dv10 of from about 14.3  $\mu\text{m}$  to about 17.1  $\mu\text{m}$  and a Dv50 of from about 31.0  $\mu\text{m}$  to about 35.3  $\mu\text{m}$ ” for intranasal delivery of an opioid. The Office action appears to acknowledge this point, but the Office action then inappropriately relies on the position that it would be “obvious to try” various permutations of numerous spray features until eventually arriving at the spray plume required in claim 53. The Office action also appears to phrase this position in terms that “it would well be within the purview of the one of skill to engineer and/or manipulate the configuration of the device in such a way as to achieve the desired spray plume.” Office action, page 3. This “obvious to try” standard has been denounced by *In re Kubin*, as noted above. Further, see *Procter & Gamble Co. v. Teva Pharmaceuticals, USA, Inc.* (Fed. Cir. 2009), 08-1404 (explaining that “patents are not barred just because it was obvious to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.”)

2. In Contrast to the Office Action’s Assertion, Applicant’s Patent Application Does Provide Data Illustrating the Superior Nasal Absorption Achieved Relative to the Prior Art Multi-dose Spray Device.

Applicant’s patent application describes, for example, the results of a comparative study using human subjects. The details of this study are described in Example 1 on pages 12-19 of the application as filed and in the Preliminary Amendment filed October 5, 2005. Further, the results of the study are shown graphically in Figures 1 and 2 of the application. The study compared plasma concentrations of butorphanol in human test subjects following intranasal administration of butorphanol tartrate using either the Bristol-Myers Squibb multi-dose spray device for STADOL®NS or the unit-dose spray device having plume geometry features captured by claim 53. Figures 1 and 2 show that the plasma concentration of butorphanol is substantially higher when the “Invention” spray device is used, relative to

the “Prior Art” spray device (The legend in Figures 1 and 2 use the term “Prior Art” to refer to the multi-dose spray device, and use the term “Invention” to refer to the unit-dose spray device.). The unique features of the spray plume for the opioid containing unit-dose spray device, as characterized by Dv10 and Dv50 parameters, are believed to provide the superior absorption of the administered drug.

Applicant believes that the description in Example 1 of the application of the study on human patients, the information presented in the Preliminary Amendment of October 5, 2005, the comparative data in Figures 1 and 2, and the further explanation provided above address the comments posed in the Office action concerning the location of experimental data in the application, the nature of the unit-dose spray device used, and how this data illustrates the benefits of the claimed invention and distinguishes the invention over the Bristol-Myers Squibb multi-dose spray device for STADOL®NS. Nevertheless, the Examiner is cordially invited to contact the undersigned attorney with any further questions.

3. Recent Federal Circuit Precedent Reiterates that the Applicant’s Patent Application May Not be Used in Support of Hindsight Reconstruction to Reject the Pending Claims as Obvious.

None of the references cited in the Office action provide any particularized guidance as to which spray plume parameters are critical, nor do these references provide any direction as to which of many possible combinations of such parameters would produce a spray plume superior for administration of an opioid containing intranasal pharmaceutical composition. The only instruction concerning the desirability of a spray plume having the features required by claim 53 is the Applicant’s own patent application. As such, the Patent Office is forbidden from taking the inventive knowledge provided by the Applicant’s own patent application and use this knowledge for hindsight reconstruction of the invention. See, for example, Procter & Gamble Co. v. Teva Pharmaceuticals. USA, Inc. (Fed. Cir. 2009), 08-1404 (cautioning against “hindsight claims of obviousness”). It is only by reading the Applicant’s own patent application that the Examiner would know to select the spray plume

required by claim 53 having a “Dv10 of from about 14.3  $\mu\text{m}$  to about 17.1  $\mu\text{m}$  and a Dv50 of from about 31.0  $\mu\text{m}$  to about 35.3  $\mu\text{m}$ ” for intranasal delivery of an opioid.

In view of the foregoing remarks, Applicant respectfully submits that the teachings of Weinstein, Levin, and Ward-Smith do not render obvious the subject matter of claim 53, and request that the rejection of claim 53 under 35 U.S.C. § 103(a) be reconsidered and withdrawn. Furthermore, because claims 54-59, 62-67, 70, and 71, depend from 53 and, therefore, incorporate all the limitations of claim 53, the remarks relating to claim 53 are reiterated here. Accordingly, Applicant also respectfully requests that the rejection of claims 54-59, 62-67, 70, and 71 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

***Rejection of Claims 60, 61 and 72 Under 35 U.S.C. § 103(a)***

According to pages 9-13 of the outstanding Office action, claims 60, 61 and 72 stand rejected under 35 U.S.C. § 103(a) as being obvious over Weinstein, Levein, Ward-Smith, Illum *et al.* in J. Pharmacol. Exp. Therapeutics (2001) 301: 391-400 (hereinafter “Illum”), Pezron *et al.* in (Expert Opin. Ther. Patents (2002) 12: 331-340 (hereinafter “Pezron”), Mansjushree *et al.* in Can. J. Anesth. (2002) 49: 190-193 (hereinafter “Mansjushree”), and U.S. Patent No. 6,127,385 to Midha *et al.* (hereinafter “Midha”). Applicant respectfully traverses the rejection.

Claims 60, 61 and 72 depend from and, therefore, incorporate all the limitations of independent claim 53. The arguments relating to claim 53 are reiterated here. Applicant submits that the applied references fail to render obvious the subject matter of claim 53. As a result, Applicant respectfully requests that the rejection of claims 60, 61, and 72, which incorporate all the limitations of claim 53, be reconsidered and withdrawn.

## CONCLUSION

Applicant believes that all rejections have been addressed, and early favorable action is respectfully solicited. The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,

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